57.(new) A vaccine as defined in claim 1 wherein the LPS is derived from N. meningtidis, H. influenzae, Moraxella catharralis, Pseudomonas aeruginosa, Salmonella enterica and Escherichia coli.

58. (new) A vaccine as defined in claim 57 wherein the LPS is derived from Salmonella enterica.

59. (new) A vaccine as defined in claim 57 wherein the LPS is derived from H. influenzae.

C16 60. (new) A vaccine as defined in claim 57 wherein the LPS is derived from N. meningtidis.

61. (new) A vaccine as defined in claim 57 wherein the LPS is derived from Moraxella catharralis.

62. (new) A vaccine as defined in claim 57 wherein the LPS is derived from Escherichia coli.

REMARKS

In paragraph 3 of the Office Action, claims 9, 11, 17 and 19-50 were rejected under 35 U.S.C.§112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Reconsideration is requested.

The basis for this ground of rejection was that certain peptides of the dependent claims did not conform to the formulas $(A)_n$; $(AB)_m$; and $(ABC)_p$ set forth in the generic claims. In response, the claims have been reviewed and where there was any possibility that the specific peptides of the dependent claims did not conform to the formulas of claim 1, these claims have been rewritten in independent form.

In response to the Examiner's query regarding whether or not the dependent claims were intended to conform to each of

the formulas $(A)_n$; $(AB)_m$; and $(ABC)_p$, it was intended that only one of these formulas was to conform to a dependent claim. It is believed that this amendment avoids the basis for the rejection of the claims under 35 U.S.C.§112, second paragraph and it is requested that this ground of rejection be withdrawn.

In paragraph 4 of the Office Action, claims 1-17, 19-34 and 51 were rejected under 35 U.S.C.§102(b) as being unpatentable over Porro.

Reconsideration is requested in view of this Amendment.

By this Amendment, all of the rejected claims have been amended so that they now include the recitation "a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide, on a weight basis relative to said LPS". Support for this recitation is found in the specification at page 6, lines 24-31.

In the Office Action, the Examiner noted that the previous claims did not recite: "stoichiometric excess of peptide relative to the lipid moiety" and that the Examiner did not suggest that phrase be added to the claims. The applicant has added the recitation --on a weight basis relative to said LPS-- which is based on the description at page 6, lines 24-32 where it was disclosed that the vaccine was prepared by combining LPS with a peptide on specific weight/weight ratios. It is believed that this language defines over the prior art description of making a vaccine in the Porro patent publication WO/95/03327 ('327 publication).

The '327 publication at page 7, lines 14-20 states that the vaccines may be made "using stoichiometric amounts of Lipid-A or LPS with the peptide". This does not disclose using a "stoichiometric excess of peptide relative to the lipid moiety" in the making of a vaccine. In the absence of a disclosure of the presently claimed concept of using a stoichiometric excess of the peptide relative to LPS, it is submitted that the claims define novel subject matter and the rejection under 35 U.S.C.§102(b) should be withdrawn.

In paragraph 5 of the Office Action, claims 1-17 and 19-

56 were rejected under 35 U.S.C.§112, first paragraph because the specification while being enabling for the LPS from S. typhi and peptide, does not reasonably provide enablement for the use of any LPS and peptide as a vaccine preparation for preventing gram-negative infections.

Reconsideration is requested.

Since the present ground of rejection has been entered under 35 U.S.C.§112 and not 35 U.S.C.§101, it is presumed that there is no issue as to lack of utility for the claimed subject matter. This response is directed to the rejection as being based on a question of whether or not one who is skilled in the art could "make and use the invention" based on the applicants's disclosure in light of contemporary knowledge in the art.

The present disclosure at pages 2 and 3 describes various peptides which may be used in the making of the vaccine. It is believed that the disclosure of useful peptides for the practice of the invention has not been questioned and that the only issue goes to the scope of the disclosure of how to use LPS from species of gram-negative bacteria which are not exemplified in the Examples.

There is no requirement that a patent application must provide a working example for each species that may be within a generically claimed invention. The disclosure of several species coupled with a general description of the scope of materials that may be used to practice the invention is all that is necessary under the provisions of 35 U.S.C.§12, first paragraph.

In the present application, the applicant has used a term, i.e. "gram-negative bacteria", that is definite and well known to those who are skilled in the art to describe the sources for LPS that may be used in the invention. At page 14 of the specification, it was explicitly noted that the vaccine could be monovalent or polyvalent with regard to the use of LPS from one species or more than one species. This clearly teaches that the LPS from each species is required to make a vaccine for that particular species.

The preferred embodiment is recited as being preferably 250 to 2500 units peptide to 1 unit bacterially-derived LPS. Preparation of a protein-conjugated LPS for use in the vaccine is taught on page 15 lines 6 et seq., and a preferred ratio of LPS to BSA is taught on page 7 lines 1-3. Details of the LPS/peptide reaction are described on page 13 lines 15-18 to page 15, line 33.

The practice of the invention is taught on page 13 lines 18-29 of the specification and a suggested regimen of initial dose plus booster doses is taught on page 13 lines 30-33. Successful in-vivo experimental use of the invention as a vaccine in mice is reported in Figures 6a and 6b as discussed on page 5 of the application. This data provides guidance to those who are skilled in the art as to how to make and use the vaccine as claimed. This is all that is required by 35 U.S.C.§ 112, first paragraph.

The Examiner noted that Bone, 1996 and Cross et al. had established that all trials of new therapies for sepsis conducted to date have failed to show efficacy. The Bone publication points out once a patient begins to develop very high systemic levels of pro-inflammatory mediators the resultant clinical syndrome of sepsis becomes very difficult to treat. The Cross et al. publication is concerned with the development of an model for testing the effectiveness of a sepsis therapy and not with the testing of a vaccine. The concluding sentence of Cross et al. states that ..."For the proper study of sepsis, study bacteria that cause sepsis". This is what the applicant has done with regard to the challenge study set forth at page 18, Table I of the present application.

The comments of Bone and Cross et al. are concerned with sepsis <u>per se</u> and there is no mention of a vaccine or how a vaccine is to be evaluated. The text of the claims has been modified to point out that what is claimed is "A vaccine for preventing gram-negative infections" as described in the specification particularly at page 3, line 16-18. Page 3, lines 14-15 have been revised to eliminate any possibility

that the phraseology used in the specification was claiming that the vaccine was a therapeutic agent for the treatment of the effects of endotoxin. The phrase "and the effects of endotoxins" has been deleted from the claims to avoid any possibility that the claims might be interpreted as being directed to treating the effects of endotoxin rather than preventing the effects of endotoxins by preventing the gram-negative infection that causes the elaboration of endotoxins.

It is believed that the amended claims properly point out the invention and that they are in compliance with the patent statute. New claims 57-61 are based on the examples and specification, particularly page 5, line 30 to page 6, line 4.

Applicant respectfully submits that based on the amendments and arguments presented that all the claims are in condition for allowance. Any additional required fee may be charged to Deposit Account No. 08-1540.

Early and favorable action is earnestly requested.

Respectfully submitted,

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Marked up copy of Specification Amendment

The vaccine is particularly useful for the prevention of gram-negative infections and prevents the effects of endotoxins produced by said gram-negative infections.

Marked up copy of amended claims:

1.(twice amended) A vaccine for preventing gram-negative infections [and the effects of endotoxins] which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide ,on a weight basis relative to said LPS, said peptide comprising:
(a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;
(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and (c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2.

10. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide ,on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises [is of the formula]: $(Lys\text{-}Phe)_5$ (SEQ ID NO: 5). $(AB)_M$

11. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:

Lys-Phe-Leu-Lys-Lys-Thr-Leu (SEQ ID NO: 6).

12. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
$(Lys\text{-}Phe\text{-}Leu)_2\text{-}Lys$ (SEQ ID NO: 7) $(ABC)_p$

13. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
$(Lys\text{-}Phe\text{-}Leu)_3\text{-}Lys$ (SEQ ID NO: 8) $(ABC)_p$

14. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1 wherein the peptide comprises:
$(Arg\text{-}Tyr\text{-}Val)_3$ (SEQ ID NO: 9) $(ABC)_p$

15. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
$(Lys\text{-}Phe\text{-}Phe)_3\text{-}Lys$ (SEQ ID NO: 10) $(ABC)_p$

16. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
$(Lys\text{-}Leu\text{-}Leu)_3$ (SEQ ID NO: 11) $(ABC)_p$

17. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
$(Lys)_6(Phe\text{-}Lys)_2$ (SEQ ID NO: 12)

19. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
Cys-Lys-Phe-Lys-Lys-Cys
s----------s (SEQ ID NO: 14)

20. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:

Lys-Phe-Lys-Cys-Lys-Phe-Lys-Phe-Lys-Cys
s----------s (SEQ ID NO: 15)

21. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
Lys-Leu-Lys-Cys-Lys-Leu-Lys-Leu-Lys-Cys
s----------s (SEQ ID NO: 16)

22. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:

Arg-Thr-Arg-Cys-Arg-Phe-Lys-Arg-Arg-Cys
s----------s (SEQ ID NO: 17)

23. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
Lys-Cys-$(Lys-Phe-Lys)_2$-Cys-Lys
s----------s (SEQ ID NO: 18)

24. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
Cys-$(Lys)_4$-$(Phe)_4$-Cys
s----------s (SEQ ID NO: 19).

26. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
Val-Lys-Ala-Leu-Arg-Val-Arg-Arg-Leu (SEQ ID NO: 21).

27. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
Lys-Ser-Leu-Ser-Leu-Lys-Arg-Leu-Thr-Tyr-Arg (SEQ ID NO:22).

28. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in

claim 1] wherein the peptide comprises:
Lys-Val-Arg-Lys-Ser-Phe-Phe-Lys-Val (SEQ ID NO: 23).

29. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide comprises:
Phe-Leu-Lys-Pro-Gly-Lys-Val-Lys-Val (SEQ ID NO: 24).

30. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:
Lys-Glu-Leu-Lys-Arg-Ile-Lys-Ile (SEQ ID No: 25)

31. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:
Lys-Trp-Lys-Ala-Gln-Lys-Arg-Phe-Leu (SEQ ID NO: 26)

32. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:
Lys-Trp-Lys-Ala-Gln-Lys-Arg-Phe-Leu-Lys (SEQ ID NO: 27)

33. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:

Lys-Arg-Leu-Lys-Trp-Lys-Tyr-Lys-Gly-Lys-Phe (SEQ ID NO:28)

34. (twice amended) A vaccine for preventing gram negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:
Lys-Thr-Lys-Cys-Lys-Phe-Leu-Lys-Lys-Cys(SEQ ID NO:31)
s - - - - - - - - - - - - s.

35. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS as defined in claim 1 wherein the peptide is of the formula:

Cys-Lys-Phe-Leu-Lys-Lys-Cys
s----------s (Seq ID NO: 30).

37. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:

Lys-Phe-Leu-Lys-Lys-Thr(SEQ ID NO: 32).

38. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:

Cys-Lys-Lys-Leu-Phe-Lys-Cys-Lys-Thr-Lys
s - - - - - - - - - - - s(SEQ ID NO: 33).

39. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a

peptide on a weight basis relative to said LPS [as defined in claim 1 wherein] the peptide is of the formula:

Cys-Lys-Lys-Leu-Phe-Lys-Cys-Lys-Thr
s - - - - - - - - - - - - s(SEQ ID NO: 34).

40. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:

Ile-Lys-Thr-Lys-Cys-Lys-Phe-Leu-Lys-Lys-Cys
s - - - - - - - - - - - - s(SEQ ID NO: 35).

41. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS
[as defined in claim 1] wherein the peptide is of the formula:

Ile-Lys-Thr-Lys-Lys-Phe-Leu-Lys-Lys-Thr(SEQ ID NO: 36).

47. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:

$(Lys)_6$Phe-Leu-Phe-Leu(SEQ ID NO:42).

49. (amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS [as defined in claim 1] wherein the peptide is of the formula:

Lys-Trp-Lys-Ala-Gln-Lys-Arg-Phe-Leu-Lys(SEQ ID NO: 44).

51. (twice amended) A method for the preparation of a vaccine for prevention of gram-negative infections [and the effects of endotoxins], said method comprising combining LPS with a stoichiometric excess of a peptide <u>on a weight basis relative to said LPS</u> comprising:

(a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;

(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and

(c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2.

54. (amended) A vaccine for preventing gram-negative infections [and the effects of endotoxins] which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of peptide:LPS where there is an excess of from [250 to 2500] <u>2 to 5000</u> times by weight of peptide, said peptide comprising:

(a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;

(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and (c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2.--

55. (amended) A vaccine for preventing gram-negative

infections [and the effects of endotoxins] which comprises a complex obtained by combining LPS in a free form or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS of the formula:

Cys-$(Lys)_5$-Cys

s----------s (SEQ ID NO: 13)